Remarks

Claims 38-44, 46-66, 74-87, and 90-94 were pending in the subject application. By this Amendment, claims 38, 39, 41, 46, 50-53, 57, and 60-63 have been amended. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 38-44, 46-66, 74-87, and 90-94 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Applicant and Applicant's representative wish to thank Examiner Zara for the courtesy of the telephonic interview conducted with Mr. Glenn Ladwig on September 24, 2007, regarding the status of the current Office Action. Examiner Zara confirmed that the rejection of the claims in the current Office Action is not final.

Claims 38-44, 46-66, 74-87, and 90-94 have been rejected under 35 USC §112, first paragraph, as lacking sufficient written description. One aspect of this rejection is directed to the rejection of the claims on the ground that subject matter in the claims pertaining to interfering RNA (RNAi) constitutes new matter. Applicant notes that the Examiner acknowledges that claims 74-87 and 90-94 do find literal support in the specification and, therefore, do find written description in the subject specification. Thus, only claims 38-44 and 46-66 are rejected for containing new matter.

Applicant respectfully maintains that the subject specification does provide sufficient written description of RNAi. As Applicant has noted in previous responses, the subject specification teaches that the inhibitor of SHIP-1 function can be a genetic construct, such as "an anti-sense oligonucleotide, an RNA aptamer capable of inhibiting SHIP enzymatic activity, an RNA aptamer capable of inhibiting a ribozyme, or another genetic construct of inhibiting SHIP activity known to those of skill in the art" (page 11, lines 10-15). The subject specification teaches that the substance that inhibits SHIP function can be a nucleic acid that hybridizes to a SHIP mRNA (page 5, lines 33-34; page 6, lines 26-27; and page 11, lines 25-26). The subject specification teaches that the delivered nucleic acid molecule can incorporate into a specified gene so as to inactivate the gene and "turn off" the product the gene was making, or to alter the translation or stability of the mRNA of the specified gene product (page 12, lines 13-16). The subject specification teaches that the nucleic acid can be either RNA or DNA, may be a non-coding sequence, and may be single-stranded or double-

stranded (page 14, lines 7-9 and 15). Furthermore, the subject specification teaches that the SHIP inhibitor can be DNA that directs production of RNA or a polypeptide that inhibits SHIP function (page 15, lines 33-34). There is no requirement that any one sentence or paragraph of the specification, standing alone, has to provide the full support for the claims. Rather, the assessment is to be made from the perspective of one of ordinary skill in the art at the time the application was filed, guided by the teachings of the specification as a whole. Based on the characteristics provided in the subject specification, one of ordinary skill in the art would immediately envision interfering RNA as a means for inhibiting translation of SHIP-1 at the time the application was filed.

In addition, it is well settled in patent law that the language used in an amendment of a claim does not have to be disclosed word for word in a specification. *In re Wilder*, 222 USPQ 369, 372 (Fed. Cir. 1984) ("It is not necessary that the claimed subject matter be described identically, but the disclosure must convey to those skilled in the art that applicant had invented the subject matter later claimed."); *In re Lukach*, 169 USPQ 795, 796 (CCPA 1971)("... the invention claimed does not have to be described in *ipsis verbis* in order to satisfy the description requirement of §112."). In addition, the Patent Office guidelines for examiners make it clear that explicit written support is not required to meet the requirements of 35 USC § 112, first paragraph. ("To comply with the written description requirement of 35 U.S.C. §112, ¶ 1, ... each claim limitation must be expressly, **implicitly**, or **inherently** supported in the originally filed disclosure." (emphasis added) See "Guidelines for Examination of Patent Applications Under 35 U.S.C. §112, ¶ 1, 'Written Description' Requirement," *Federal Register* Vol. 66, No. 4, pp. 1099-1111, at page 1107, first column, lines 10-17). Thus, support for a claim limitation can be implicit or inherent in the disclosure of a patent application.

However, by this Amendment, Applicant has amended claims 38-44 and 46-66 to delete reference to "interfering RNA." Claims 38-44 and 46-66, as amended, refer to an RNA specific for a SHIP-1 mRNA wherein the RNA interferes with transcription and/or translation of the SHIP-1 mRNA. Support for the amendment can be found throughout the subject specification including, for example, at page 5, lines 29-30, and page 9, lines 10-15. Accordingly, Applicant respectfully asserts that the "new matter" rejection is rendered moot.

Also under this rejection, the Examiner rejects the claims on the ground that the subject specification does not provide sufficient written description to reasonably convey to an ordinarily skilled artisan that Applicant had possession of the claimed subject matter. The Examiner maintains that the specification and claims do not adequately describe the concise structural features that distinguish structures within the claimed genus from those without (*e.g.*, the nucleotide sequences or a representative number of RNAi molecules of the generic RNAi structures claimed, which specifically bind mouse or human SHIP-1 mRNA and which hybridize *in vitro* under conditions of stringency and hybridize *in vivo* with mouse or human SHIP-1 mRNA, and which inhibit SHIP-1 function *in vivo*, and which suppress graft-versus-host disease and transplant rejection). Applicant respectfully maintains that the subject specification does provide sufficient written description to establish that Applicant was in possession of the claimed invention.

Under this rejection, the Examiner asserts that the Declaration filed July 21, 2004, which discloses SiRNA molecules and their inhibition of expression of SHIP-1 *in vitro* and *in vivo*, dose not overcome the "failure to provide support for RNAi in the original application." Applicant respectfully asserts that the subject specification does provide disclosure of interfering RNA, as noted previously herein. The evidence submitted in the Declaration is evidence that Applicant was in possession of the claimed invention, *i.e.*, an RNA specific for SHIP-1 mRNA wherein the RNA interferes with transcription and/or translation of the SHIP-1 mRNA. Submission of post-filing evidence has long been accepted under U.S. patent law.

The Examiner also asserts under this rejection that the disclosure of "two species with the broad genus of RNAi molecules claimed" are not sufficiently representative of the genus to provide written description of the genus under 35 USC §112, first paragraph. The teaching of the subject specification and the knowledge of the sequence and structure of the SHIP-1 gene provide one skilled in the art with a sufficient structural template and functional correlates to describe the genus of RNA that interfere with transcription and/or translation of SHIP-1 mRNA and hybridizing nucleic acid molecules that suppress expression of the SHIP-1 gene in human or mouse hematopoietic cells. The teaching of the subject specification, the knowledge of the sequence and structure of the SHIP-1 gene, and the mechanism by which the recited molecules inhibit gene expression, together provide sufficient structural and functional correlates to demonstrate possession of the RNA and hybridizing

nucleotides recited in the claims. Identification of specific RNA and specific hybridizing nucleotides would not just be likely, it would be inevitable and imminent. All functional descriptions of genetic material do not necessarily fail to meet the written description requirement as a matter of law. Rather, the Court has held that the written description requirement may be satisfied if, in the knowledge of the art, the disclosed function is sufficiently correlated to a particular, known structure. *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 963; 63 USPQ2d 1609, 1613 (Fed. Cir. 2002). Such is the case here. The written description requirement must be considered in the context of the claimed invention and the state of knowledge in the relevant art. *Capon et al. v. Eshhar et al.*, 418 F.3d, 1349 (Fed. Cir. 2005).

The fundamental concept of the invention is that SHIP-1 deficiency would be of therapeutic benefit in suppressing transplant rejection and graft-versus-host disease (GVHD), as taught in the subject application. Furthermore, Applicant has shown that only partial SHIP-1 deficiency in the myeloid lineage is required to achieve significant suppression of allogeneic T cell responses, which mediate GVHD and graft rejection. The state of the art was sufficiently developed such that tools for inducing the required SHIP-1 deficiency were appreciated by the inventor, taught in the patent application, and available to those of ordinary skill in the art. Thus, the applicant submits that the patent application contains sufficient disclosure to convey to one of ordinary skill in the art that the applicant had possession of the concept of what is claimed, which is all that is necessary to satisfy the written description requirement of 35 USC §112, first paragraph.

In view of the above remarks and amendments, reconsideration and withdrawal of the rejection under 35 USC §112, first paragraph, is respectfully requested.

Claims 38-44, 46-66, 74-87, 90-92, and 94 have been rejected under 35 USC §112, first paragraph, as non-enabled by the subject specification. Under this rejection, the Examiner asserts that the subject specification does not enable inhibiting SHIP-1 *in vivo* comprising the administration of any RNAi specific for SHIP-1 mRNA present in human or mouse hematopoietic cells, or comprising the administration *in vivo* or *ex vivo* of any nucleic acid molecule that hybridizes *in vitro* under conditions of stringency with human or mouse SHIP-1 mRNA or that hybridizes *in vivo* with SHIP-1 mRNA present in mouse or human hematopoietic cells, nor of suppressing a transplant rejection in any patient, or treating graft versus host disease (GVHD) in any patient comprising the

administration of any interfering RNA specific for SHIP mouse or human mRNA. The Examiner further asserts that the art of gene therapy, at the time of the instant application, was a highly unpredictable endeavor requiring undue experimentation. Applicant respectfully asserts that the subject specification does enable the claimed invention.

As Applicant has noted previously, consideration is to be given to post-filing date evidence (*e.g.*, Declarations and Exhibits) offered by Applicant to show that the claimed invention works, provided that the evidence is consonant with the teachings of the specification as filed. In making this determination, the Examiner is to compare the materials and methods used in the experiments of the Declaration and Exhibits with those taught in the application to make sure that they are commensurate in scope. This means that the Examiner is to confirm that the experiments used the guidance in the specification as filed and what was well known to one of skill in the art (MPEP §2164.05). Thus, the requirement of consonance between the submitted evidence and the teachings of the specification is not evaluated in a vacuum. Rather, the determination is to be made from the standpoint of one of ordinary skill in the art. Thus, the knowledge possessed by those persons of ordinary skill in the pertinent art of nucleic acid delivery, for example, must be considered. A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which the invention pertains to make and use the invention as of its filing date. *In re Glass,* 492 F.2d 1228, 181 USPQ 31 (CCPA 1974). As iterated in MPEP 608.01(p), the prior art setting may be mentioned in general terms. It is "the essential novelty, the essence of the invention, [that] must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention."

The enablement requirement of 35 USC §112, first paragraph, does not require that Applicant reinvent the wheel. There is no need to inform the layman nor disclose what one of ordinary skill in the art already possesses.

> Paragraph 1 permits resort to material outside of the specification in order to satisfy the enablement portion of the statute because it makes no sense to encumber the specification of a patent with all the knowledge of the past concerning how to make and use the claimed invention. One skilled in the art knows how to make and use a bolt, a wheel, a gear, a transistor, or a known chemical starting material. The

> specification would be of enormous and unnecessary length if one had to literally reinvent and describe the wheel. *Amtel Corporation v. Information Storage Devices, Inc.*, 198 F.3d 1374; 53 USPQ2d 1225 (Fed. Cir. 1999).

As the Examiner is aware, the quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" *In re Wands*, 858 F.2D 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). Time and expense are merely factors in this consideration and are not the controlling factors. *United States v. Telectronics Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). MPEP §2164.06. Even "tedious and laborious" experimentation is not necessarily undue experimentation for purposes of enablement under 35 USC §112, first paragraph. *Ex parte Erlich* 3 USPQ2d 1011 (BPAI 1982).

The evidence of record shows that nucleic acid molecules, such as interfering RNA, can be successfully delivered to cells *in vitro* and *in vivo*, and achieve the required level of SHIP-1 knockdown established with the SHIP-1 knockout models. Applicant respectfully submits that, in view of the state of the art of nucleic acid delivery at the time the application was filed, one of ordinary skill in the art would be able to make and deliver agents, such as interfering RNA, to human cells *in vitro* and *in vivo*, without the need for undue experimentation.

Under this rejection, the Examiner further asserts that the subject specification does not teach a representative number of species from the genus of inhibitory compounds that provide for treatment effects following administration to the organism. The Examiner asserts that Applicant's showing of three species of the claimed genus and their use in a mouse model are not representative or correlative of the ability to achieve *in vivo* SHIP-1 inhibition or subsequent treatment effects. Applicant respectfully asserts that a representative number of species are taught by the subject

specification. An applicant for patent is not required to teach every species, or even a majority of species, of a claimed genus in order to satisfy the enablement requirement of 35 USC §112, first paragraph. The Examiner acknowledges that Applicant has taught three species within the genus. Applicant respectfully asserts that a person of ordinary skill in the art, having the benefit of the teachings of the subject specification, could readily make and use these species, as well as other species within the scope of the claimed invention, without resort to undue experimentation. Applicant respectfully submits that while some experimentation may be necessary, it is not controlling on the issue of undue experimentation. *Ex parte Jackson*, 217 USPQ 804, 807 (Bd. Pat. App. & Int. 1982) ("The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine . . .") (emphasis added). Moreover, Applicant respectfully asserts that the evidence provided in the subject specification is correlative of the ability to achieve *in vivo* SHIP-1 inhibition and subsequent treatment effects. Applicant respectfully asserts that suppression of graft rejection in mice or abrogation of GVHD in mice using the claimed invention would be reasonably predictive of the results that could be obtained in humans. The Examiner has not provided any evidence to suggest that the mouse model is not correlative of results in humans. It is well accepted in patent law that evidence of efficacy in humans is not required where there is an acceptable animal model that is reasonably predictive of human disease or conditions.

Accordingly, reconsideration and withdrawal of the rejection under 35 USC §112, first paragraph, is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicant's agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, Applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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Attachment: Petition and Fee for Extension of Time